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The effect of cocaine on the expression of motor activity and conditioned place preference in high and low alcohol-preferring Wistar rats

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Abstract

Outbred rats show significant variability in their propensity to consume alcohol. These experiments were designed to examine the effect of cocaine on the expression of motor activation or place preference in outbred Wistar rats that consumed either high or low quantities of alcohol. These rats were exposed to a 2-bottle limited access procedure and dichotomized into 2 groups, high (mean 0.91 g/kg/h) and low alcohol consumption (0.36 g/kg/h), and then exposed to repeated daily cocaine, 10 or 20 mg/kg, or saline injections. The low alcohol-consuming rats showed a significant increase in motor behavior to a cocaine challenge across both doses of cocaine, which did not differ from each other. The high alcohol-consuming rats showed a significant increase in motor behavior only at the high dose of cocaine. In Experiment 2 both high and low alcohol-consuming rats were exposed to a conditioned place preference procedure using cocaine 10 mg/kg. High alcohol-consuming rats showed a significant place preference to the cocaine-paired side while low consuming rats did not. The differential effects of cocaine on motor activating behavior and reward obtained in these experiments suggest that those factors determining whether an outbred Wistar rat will consume high or low amounts of alcohol are related, in part, to differential sensitivity of those neural systems underlying the effects of those drugs.

Keywords: Alcohol preference; Cocaine; Motor behavior; Place preference

1. Introduction

The reinforcing properties of drugs are most typically inferred from self-administration studies that provide the animal with some mechanism of control over intake of the drug either through a two-bottle preference test or an operant approach with drug delivery made contingent upon some response output from the animal. In the case of alcohol, alcohol-preferring and nonpreferring strains of rats have been developed using these techniques to identify high and low consumers using selective breeding. These alcohol-preferring strains, developed from outbred heterogeneous stock selected for their alcohol preference, are hypothesized to exhibit some of the same critical differences assumed to underlie alcohol use in that subset of the clinical population who are at risk for alcoholism.

The selection process, that develops high and low alcohol-consuming strains, reduces both the biological and behavioral variability of outbred strains. While this has utility for the development of animal models, humans are heterogeneous, even among that subset of the general population defined by dependence on alcohol or other drugs there is substantial variability. While the use of alcohol-preferring and nonpreferring strains has increased in recent years, most experiments focusing on the reinforcing properties of alcohol use heterogeneous outbred strains of rats. Our laboratory uses heterogeneous outbred Wistar rats and we have found over time that ~25% to 33% of the rats in a typical group received from a vendor will consist of those that will not drink pharmacologically meaningful amounts of alcohol. Because we are interested in assessing the pharmacotherapeutic potential of drugs on the prevention of relapse in alcoholics, we use only those rats that drink pharmacologically meaningful amounts of

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alcohol. While this strategy has worked well, the question remains as to what factors underlie the observed difference in alcohol preference. Those factors could include a pre-ingestional variable such as taste or a postingestional variable related to the sensitivity of those neural systems underlying the reinforcing properties of alcohol.

At the clinical level many alcoholics have comorbid dependencies on drugs other than alcohol. Often these drugs have psychomotor stimulant properties. For example, in alcohol-dependent patients 20% to 30% were also found to qualify as cocaine-dependent (Miller and Giannini, 1991). These data suggest common linkages between drugs like cocaine and alcohol. One relationship held in common between these drugs is their dependence on the response of the mesolimbic dopamine system to produce the positive reinforcing or reward properties (Koob, 1992). A role for other neural systems underlying the reinforcing properties of addictive drugs has also been identified. Our laboratory has demonstrated that manipulation of GABAergic pathways decreases the concurrent oral consumption of both alcohol and cocaine (Stromberg et al., 2001), while manipulation of opioidergic pathways affected the consumption of alcohol but not cocaine (Stromberg et al., 2002). The differential response on alcohol and cocaine consumption produced by disruption of different neural systems may provide suggestions as to why only a subset of the population is susceptible to comorbid abuse of both alcohol and cocaine, but a common feature that remains is that both drugs activate the mesolimbic dopamine system. Differences in both GABAergic and opioidergic systems have been identified between alcohol-preferring and nonpreferring strains of rats (see Li, 2000 for review). Differences have also been identified in dopamine receptor density and the response of this system to alcohol in selectively bred high and low alcohol-preferring strains has been established (Honkanen et al., 1999; McBride et al., 1995). In addition, in Wistar rats identified as high alcohol consumers exposure to alcohol induces a greater dopamine response in the nucleus accumbens than in Wistar rats identified as low consumers (Engel et al., 1992). This suggests that a differential sensitivity in the mesolimbic dopamine system may be a common factor underlying the behavioral response to alcohol and cocaine.

Another way of examining the question of the relationship between alcohol and cocaine is to ask if there is a difference in the response to cocaine in a behavior other than drug self-administration in rats with a history of either high or low alcohol consumption. These experiments were designed to examine the effect of both the unconditioned and conditioned effects of cocaine in high and low alcohol-consuming Wistar rats. Experiment 1 was designed to examine the effect of repeated high or low doses of cocaine on the motor output of Wistar rats with a consumption history of either high or low quantities of alcohol. Experiment 2 used a conditioned place preference procedure pairing cocaine with a contextual stimulus, which then acquires secondary reinforcing properties through a Pavlovian association. A key difference between this measure and that used in Experiment 1 is related to its reliance on drug-associated cues presented in the absence of drug at time of test. We hypothesized that rats with a differential history of alcohol consumption would demonstrate different behavioral responses to cocaine in both motor output and place preference.

2. Material and methods

2.1. Subjects

Thirty-six male Wistar rats in Experiment 1 and twelve in Experiment 2 purchased from Harlan (Indianapolis, IN) weighing between 250 and 275 kg upon arrival were housed in individual acrylic cages in a temperature-controlled (22 °C) animal colony on a 12 h/12 h reverse light/dark cycle with lights out from 0700 to 1900. Animals were provided with ad libitum food and water throughout the entire experiment. All research was approved by the Institutional Animal Care and Use Committee at the Philadelphia VAMC and was conducted according to *The Guide for the Care and Use of Laboratory Animals* as adopted by the National Institutes of Health.

2.2. Apparatus for locomotor tests

All behavioral procedures were conducted in open field test apparatus (43.2 × 43.2 cm), Med Associates, St. Albans, VT 05478. All behavior was recorded as breaks in photobeams recorded with Med Associates interface, software, and computer.

2.3. Apparatus for conditioned place preference tests

All procedures were conducted in a three Compartment Conditioned Place Preference Chamber (67.9 × 21 × 20.9 cm) Med Associates St. Albans, VT 05478. This unit consists of a black side with grid floor, a white side with a mesh floor, separated by a grey center chamber. All behavior was automatically recorded by photobeam using Med Associates interface, software, and computer.

2.4. Procedure for locomotor tests

Rats were allowed to acclimate for 1 week after arriving in the laboratory. They were then exposed to a continuous two-bottle choice of water and an ascending alcohol concentration (2% for 2 days, 4% for 2 days, and 6% for the remainder of the experiment). Rats were maintained on the continuous two-bottle choice procedure until consumption of the 6% alcohol solution reached stability. The stability criterion used in these experiments was no deviation in consumption greater than 20% across 5 consecutive days. Once stability was reached, the alcohol bottles were removed from the cages, and on the following days the rats were given 1-h access to both alcohol and water. The rats were weighed daily before the 1-h limited access period, and the water and alcohol bottles were weighed to the nearest 0.1 g both before and after the limited access session. The rats were continued on the limited access procedure until the stability criterion was reached. This phase typically lasted between 30 and 40 days. Rats were removed

from alcohol for the balance of the experiment and identified as high or low consumers and randomly assigned to high (mean=0.91 gm/kg/h, range 0.66 to 1.44 gm/kg/h) or low (mean=0.36 gm/kg/h, range 0 to 0.48 gm/kg/h) groups. A period of 7 to 14 days intervened between alcohol exposure and cocaine exposure. Within each group rats were randomly assigned to a saline or cocaine 10 or 20 mg/kg condition ($n=6$). All rats were exposed to a baseline saline injection day followed by 4 consecutive treatment days and finally 7 days later a persistence test day. Treatment consisted of 0, 10 or 20 mg/kg cocaine injected IP in a volume of 1.0 ml/kg immediately before exposure to a Med Associates open field test apparatus. Persistence test consisted of saline for the saline group or a 5 mg/kg cocaine challenge for both cocaine treatment groups.

2.5. Procedure for conditioned place preference tests

All procedures involving exposure to alcohol were identical to those used in Experiment 1. Rats were identified as high alcohol consumers ($n=6$) or low alcohol consumers ($n=6$) as in Experiment 1. For the conditioned place preference test rats were placed in the central neutral compartment and confined for 5 min at which time the automatic guillotine doors opened and the rats were given 15 min access to the entire apparatus. Time spent in each of the three compartments was recorded as the baseline value. An unbiased CPP was used and half of the rats were randomly assigned to the white compartment and half to the black compartment for cocaine injections with saline administered on the opposite side following the initial baseline measure. Over the next 8 days rats were injected with either saline or cocaine 10 mg/kg and confined to their assigned compartment for 30 min. The order of drug and saline presentation was counterbalanced across rats so that half of the rats received saline on the first day and the other half cocaine on the first day. Saline or cocaine injections alternated over days so that each rat received 4 saline and 4 cocaine pairings in their assigned chambers. On the tenth day rats, in the absence of drug, rats were again placed in the center neutral compartment and after 5 min were allowed access to the entire chamber for 15 min. Time spent in each compartment was recorded. The preference for the cocaine-paired compartment was then compared to the baseline preference value to determine shift in preference.

2.6. Drugs

Alcohol was mixed with tap water to yield a 6% (vol/vol) solution and cocaine (Sigma, St. Louis) was mixed with physiological saline to yield doses of 5.0, 10.0, and 20.0 mg/kg and was injected in a volume of 1.0 ml/kg immediately before being placed into open field test apparatus.

2.7. Data analysis

Data for both the high and low alcohol consumers were initially analyzed using a repeated measures ANOVA design that compared cocaine dose 0, 10, or 20 mg/kg repeated across the initial saline injection day, the four saline or cocaine injection days, and the test injection day. Where appropriate this was followed by Tukey post hoc tests to determine differences between groups. In Experiment 2, the baseline side preference score for the cocaine-paired chamber was compared to the preference score for the same chamber at final test and converted to a preference change score (final test preference − baseline preference = preference change score) and analyzed using *t*-tests.

3. Results

3.1. Experiment 1

For both the high and low alcohol consumers the high dose of cocaine was significantly different than saline, while the low dose of cocaine was only different from saline only in the low alcohol consumers. Fig. 1 Panel A shows the effect of saline or cocaine on ambulatory responses for the high alcohol consumers across the six days of the experiment. A repeated measures ANOVA of the three groups, 0, 10, or 20 mg/kg cocaine measured across the six treatment days yielded a significant effect for dose [$F(2,108)=18.29$, $p=.000009$], a significant effect for treatment day [$F(5,108)=4.34$], and a significant dose by treatment day interaction [$F(10,108)=4.57$, $p=.000022$]. Subsequent Tukey post hoc tests revealed that the

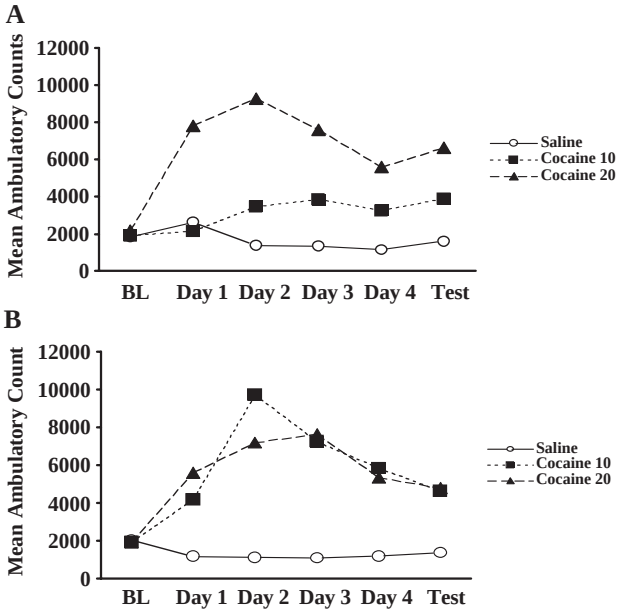

Fig. 1. Panel A: Mean ambulatory counts in high consuming alcohol rats in the saline, cocaine 10 mg/kg, and cocaine 20 mg/kg groups. BL is saline baseline day, d1 through d4 represent individual drug or saline treatment days, and test represents the persistence test day. *Designates that the 20 mg/kg group differed significantly from both the 10 mg/mg cocaine and saline groups ($p<0.05$). Panel B: Mean ambulatory counts in low consuming alcohol rats in the saline, cocaine 10 mg/kg, and cocaine 20 mg/kg groups. BL is saline baseline day, d1 through d4 represent individual drug or saline treatment days, and test represents the persistence test day. *Designates that both the 10 and 20 mg/kg group cocaine groups differed significantly the saline groups ($p<0.05$).

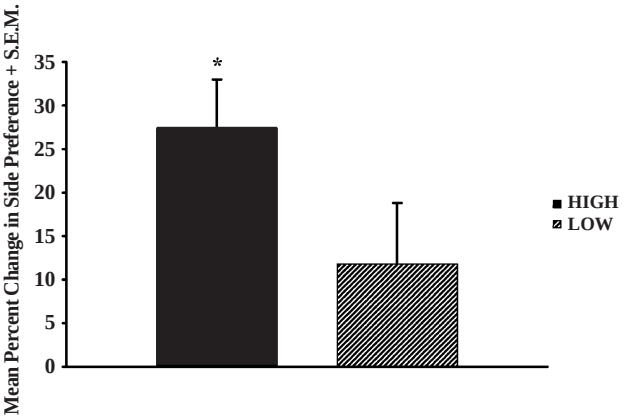

Fig. 2. Mean shift in cocaine-paired side preference between high and low consuming alcohol rats between baseline and test days (+SEM). *$p<0.05$.

20 mg/kg cocaine dose differed from both the 10 mg/kg cocaine dose and saline, which did not differ from each other. Fig. 1 Panel B shows the effect of saline or cocaine on ambulatory responses for the low alcohol consumers across the six days of the experiment. A repeated measures ANOVA of the three groups, 0, 10, or 20 mg/kg cocaine across the six treatment days yielded a significant effect for dose [$F(2,108)=26.54$, $p=.000001$], a significant effect for treatment day [$F(5,108)=7.38$], and a significant dose by treatment day interaction [$F(10,08)=4.57$, $p=.000022$]. Subsequent Tukey post hoc tests revealed that both the 10 and 20 mg/kg cocaine doses differed from saline but did not differ from one another.

3.2. Experiment 2

Animals in both the high and low alcohol groups showed an increase in the amount of time spent in the previously cocaine-paired compartment. Fig. 2 shows the shift in time spent on the cocaine-paired side on test day 10 for both the high and low alcohol-consuming groups expressed as a mean percent change score from the day 1 baseline values. Studentized t-tests revealed that the preference shift for the high alcohol-consuming group was significant [$t(5)=5.210$, $p=.003$], while the shift for the low alcohol consumers was nonsignificant.

4. Discussion

The key finding of these experiments is that Wistar rats with a history of high alcohol consumption are more sensitive to the reinforcing properties of cocaine but less sensitive to the motor enhancing effects of cocaine than Wistar rats with a history of low alcohol consumption. These data suggest that cocaine's effect on motor response and reward is mediated by different neural pathways. The question of what mechanisms underlie the expression of cocaine enhanced motor activation and conditioned place preference is complex. Clearly, the mesolimbic dopamine system plays a key role in the expression of both behaviors as well as alcohol self-administration. Repeated administration of cocaine has been shown to produce neuroadaptations in dopamine neurons in the VTA, nucleus accumbens, and prefrontal cortex, as well as dopaminergic neurons in the substania nigra and striatum (see White and Kalivas, 1998 for review). Most of these same dopaminergic pathways have also been shown to be involved with exposure to alcohol (Gonzales et al., 2004). In addition, specific proteins modulating neuroplasticity in neural systems other than dopamine within the nucleus accumbens and related to dopamine tone are critical for the expression of both cocaine- and ethanol-induced behaviors (Szumlinski et al., 2005). These findings suggest a relationship between the expression of behaviors mediated by these systems including drug self-administration, measures of place preference, and motor activation.

There is one other report that we are aware of that examined amphetamine-induced hyperlocomotion in Wistar rats with a history of high and low alcohol preference. In this report, while both the high and low alcohol-consuming rats showed increased activity following amphetamine, 1 mg/kg, the high consuming rats showed a significantly greater increase in activity (Fahlke et al., 1995). Unlike the procedures in the experiments reported here, which used chronic injections of cocaine, the procedure reported by Fahlke et al. used a single acute injection of amphetamine. The problem with acute drug administration is that animals can show a differential stress response depending on the degree of habituation to environmental novelty. Rats with a greater response to novelty demonstrate enhanced activity to the drug compared to rats with a lower novelty response during the first few trials; this difference then equalizes following environmental habituation after repeated trials (Russell and Pihl, 1978). Fahlke et al. report that the high alcohol-preferring rats had a significantly greater corticosterone response following amphetamine administration compared to the low alcohol-preferring rats. Those results may then be a measure of the drug effect on locomotor behavior in interaction with a stress or novelty response.

In addition, rats that have had a prior history of alcohol consumption may become cross-sensitized to psychomotor stimulant drugs. Cross-sensitization between drugs of different classes has been reported and suggests that common neural mechanisms underlie the effects of several drugs (Kalivas and Stewart, 1991). Cross-sensitization may explain why amphetamine-induced hyperactivity was greater in the high alcohol-preferring rats than in the low preferring rats (Fahlke et al., 1995). In another report, prior alcohol exposure did not yield evidence of sensitization to the rewarding effects of cocaine as measured by CPP (Le Pen et al., 1998). Similarly, the results of the present experiments don't show any evidence of cross-sensitization. Instead, in Experiment 1 of this report the high alcohol-consuming rats are less sensitive to the motor activating effects of the lower dose of cocaine than are the lower alcohol-consuming rats. The pattern of the data suggests that prior alcohol consumption of the high alcohol consumers has produced tolerance to the motor activating effects to the low dose of cocaine. However, in Experiment 2 this same dose of cocaine induced a significantly greater CPP in the high alcohol-consuming rats, when compared to the low alcohol consumers.

Differences in the expression of behavioral sensitization and CPP have also been reported in rat strains that differ in measures of drug self-administration. In one report, differential effects of cocaine emerged between Lewis and Fischer F344 rats with Lewis rats showing enhanced effects of cocaine in both measures of cocaine-induced motor enhancement and the expression of cocaine-induced CPP (Kosten et al., 1994). These findings were consistent across all doses tested for the Lewis but not the Fischer F344 rats. This suggests Lewis rats, that self-administer more drug, including alcohol, when compared to Fischer F344 rats, are also more sensitive to the motor activating effects and the cue-elicited reward effects of cocaine. However, other evidence has shown increased amphetamine-induced locomotion in F344 Fischer rats compared to Lewis rats (Stohr et al., 1998). These same authors also report that F344 Fischer rats expressed a higher amphetamine-induced place preference shift.

In support of the results reported by Stohr et al., selectively bred alcohol-nonpreferring NP rats have been shown to have higher amphetamine-induced locomotor activity when compared to alcohol-preferring P rats (McKinzie et al., 2002). These results, measuring the motor effects of amphetamine, differ from the alcohol consumption differences expressed by these two strains that are assumed to reflect the reward value of alcohol. Critical differences underlying alcohol preference have been identified in those neural pathways critical for the expression of drug preference. For example, the alcohol-preferring P rats have been found to have deficits in most major neurotransmitter systems when compared to NP rats. Specifically, in the alcohol-preferring P rats and high alcohol drinking HAD rats lower contents of dopamine have been found in the mesolimbic system (McBride and Li, 1998). This appears inconsistent with the data showing that response of these dopaminergic neurons in the mesolimbic pathway is responsible for the positive reinforcing effects of alcohol underlying those preference differences in preferring and nonpreferring strains (Koob et al., 1998). The findings in P and NP rats are consistent with similar findings in the Sardinian alcohol-preferring and nonpreferring rats. In these inbred strains the nonpreferring sNP rats were more sensitive to amphetamine-induced increase in motor behavior compared to the alcohol-preferring sP rats (D'Aquila et al., 2002). These authors also hypothesize that this difference is due to the reduced dopamine receptor density in the nucleus accumbens of sP rats.

These data suggest a paradox, i.e., rats showing a greater preference for and consumption of alcohol also show a decreased sensitivity to the locomotor activating properties of psychomotor stimulant drugs. One suggestion made to account for this seeming paradox is that alcohol-preferring rats consume more alcohol to compensate for the lower density in dopamine receptors in the nucleus accumbens. This, in turn, increases the activity of the mesolimbic system towards a level approaching normal (D'Aquila et al., 2002; McKinzie et al., 2002). Similar differences in the sensitivity of the mesolimbic dopamine system may underlie the differences in alcohol preference found in the heterogeneous Wistar stock used in the experiments reported here, but no direct measures of these systems were taken. Also, because the high and low alcohol-consuming rats in the present experiments necessarily had differential exposure to alcohol before exposure to cocaine, the effect of cross-tolerance between alcohol and cocaine can not be entirely ruled out. Further, while the cocaine data obtained suggest that postingestional factors such as an underlying difference in the sensitivity in those neural systems underlying cocaine and alcohol reward are responsible for high or low alcohol consumption, pre-ingestional factors such as taste cannot be entirely excluded.

In conclusion, this study was designed to examine underlying differences in the alcohol preference of outbred Wistar rats by evaluating the behavioral response to cocaine. The results suggest that drug reinforcement and motor activating effects are mediated by different neural systems. Alcohol preference may predict the reinforcing value of other drugs but not their motor enhancing effects.

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